Emergencies in HIV Medicine – Part I

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Abstract

Human immunodeficiency virus (HIV) infection is now a chronic manageable disease due to which it is imperative for reviewing various medical emergencies which an individual case may encounter. Emergencies may occur at any stage of the disease. HIV infection is associated with several opportunistic infections/malignancies that may be life threatening and need quick intervention by health care workers. These emergencies could be related to opportunistic infections that are seen at presentation or that occur as the immune system gets weaker, or may be HIV induced diseases like enteropathy and wasting, diarrhea leading to dehydration and its sequel, neurological complication like PML etc. and from complications resulting from use of anti-HIV medication like lactic acidosis, pancreatitis, bone marrow suppression and may include the immune reconstitution syndromes.

INTRODUCTION

In a short span of two and a half decade, HIV/AIDS has emerged as second largest killer disease that has affected mankind. The estimated number of persons living with HIV worldwide in 2007 was 33.2 million [30.6–36.1 million]. New, more accurate estimates of HIV indicate that approximately 2.5 million (2 million–3.1 million) people in India were living with HIV in 2006, with national adult HIV prevalence of 0.36%. Although the proportion of people living with HIV is lower than previously estimated, India’s epidemic continues to affect large numbers of people.

Millions and millions of dollars have been spent on research for a novel therapeutic approach/vaccine for HIV. The triple drug anti retro viral therapy (ART) has ensured a reasonably good quality of life to HIV infected individuals. However, it has been seen that HIV infection is diagnosed most of the times with one or the other opportunistic infection (OI), particularly in the developing countries. At time of diagnosis, most of the patients have advanced disease and are at a higher risk of serious OI and death.

Once HIV has entered the body, the immune system initiates anti-HIV antibody and cytotoxic T cell production. However, it can take one to six months for an individual exposed to HIV to produce measurable quantities of antibody. The immune response is weakened as memory T cells (CD4+ CCR5+) are destroyed. HIV enters the body and binds to dendritic cells (orange cells with projections) which carry the virus to CD4+ T cells in lymphoid tissue establishing the infection. Virus replication accelerates producing massive viremia and wide dissemination of virus throughout the body’s lymphoid tissues. An immune response against virus causes some protection but a chronic persistent infection is established. The production of cytokines and cell divisions that regulate the immune response for protection also cause HIV replication. There is a rapid turnover of CD4+ T cells that ultimately leads to their destruction and to a change in lymphoid tissues that prevent immune responses.

The resultant fall of the CD4 counts due to human immunodeficiency virus (HIV) infection is associated with several opportunistic infections/malignancies that may be life threatening and need quick intervention by health care workers. These emergencies could be related to

1. Opportunistic infections that are seen at presentation or that occur as the immune system gets weaker.
2. HIV induced diseases like enteropathy and wasting, diarrhea leading to dehydration and its sequel, neurological complication like PML etc.
3. Complications from the use of anti-HIV medication like lactic acidosis, pancreatitis, bone marrow suppression etc
4. Immune reconstitution syndromes.

Emergencies in HIV-infected patients can occur at any stage of the disease. Opportunistic infections may lead to irreversible damage of organs such as the brain, the eye or the lung. The use of antiretroviral therapy may be associated with side effects of ARV drugs like jaundice, lactic acidosis, anaemia etc. The drug-drug interaction can frequently lead to severe symptoms such as nausea, diarrhoea and complications such as anaemia or leucopenia.
Table 1: Emergencies in HIV infection

<table>
<thead>
<tr>
<th>Emergencies due to Opportunistic infections</th>
<th>Emergencies related to ARV therapy</th>
</tr>
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<tbody>
<tr>
<td><strong>Pulmonary emergencies</strong></td>
<td><strong>Emergencies related to ARV therapy</strong></td>
</tr>
<tr>
<td>1. Pneumocystis carinii pneumonia</td>
<td>- lactic Acidosis</td>
</tr>
<tr>
<td>2. Bacterial pneumonias</td>
<td>- Hepatic necrosis due to Nevirapine</td>
</tr>
<tr>
<td><strong>Central nervous system emergencies</strong></td>
<td>- Bone marrow suppression</td>
</tr>
<tr>
<td>1. Cerebral toxoplasmosis</td>
<td>due to zidovudine-</td>
</tr>
<tr>
<td>2. Cryptococcal meningitis</td>
<td>- Rash by NNRTI</td>
</tr>
<tr>
<td>3. Tubercular meningitis</td>
<td>o Maculopapular rash</td>
</tr>
<tr>
<td>4. PML</td>
<td>o Stevens-Johnson Syndrome</td>
</tr>
<tr>
<td>5. Primary CNS Lymphoma</td>
<td>o Abacavir hypersensitivity reaction</td>
</tr>
<tr>
<td><strong>Diarrheal diseases</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Ocular emergencies</strong></td>
<td></td>
</tr>
<tr>
<td>1. Cytomegalovirus retinitis</td>
<td></td>
</tr>
<tr>
<td>2. Varicella zoster</td>
<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathy due to IRIS causing</td>
<td></td>
</tr>
<tr>
<td>Compression on trachea, spine etc</td>
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</tbody>
</table>

At the beginning of the HIV epidemic, the incidence of the complications considered as emergencies was high in developed countries but with the advent of new therapeutic strategies the frequency of such complications and the associated need for emergency treatment has decreased drastically. In developing countries where management resources remain limited, HIV/AIDS patients are still exposed to the risk of serious complications. However very few studies have documented the emergency admissions due to HIV/AIDS in medical emergencies of hospitals in developing countries.

In a prospective study conducted in Cote d'Ivoire in 1999-2000, it was found that the most frequent reasons for emergency consultation were deterioration of general condition (62%), diarrhea (39.1%) and cough (20.5%). Illness was chronic in 54% of cases. Physical signs were severe weight loss (84%), fever (50%), pale conjunctivias (29%), respiratory signs (19.2%) and dehydration (19%). The most frequent organic involvement causing admission was digestive (39.7%), neurological (24.4%) and pulmonary (20.5%). Most medical emergencies related to the HIV infection in the adult involved opportunistic diseases.

Another study from Spain has documented pulmonary causes in 40% of emergency admissions in the HIV infected. They also found that majority of persons were from category C i.e. advanced immunosuppression.

An overview of the various emergencies in HIV infected individual are summarized in the following Table 1.

As far as the infectious conditions are concerned, the level of immunosuppression often assists in the raising the suspicion for the possible cause. Certain infections, often occur after a particular level of immunity (represented by the CD4 count) is surpassed. This will be further clarified by the following Table 2.

The present article deals with the emergencies due to the opportunistic infection. The medical emergencies encountered due to ARV therapy itself, shall be discussed in the second part of the article.

Table 2 : Relation of the occurrence of various OI with CD4 counts

<table>
<thead>
<tr>
<th>Any CD4 level</th>
<th>Kaposi Sarcoma, Pul TB, HZV, Bacterial Pneumonia, Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 250/cmm</td>
<td>PCP, esophageal candidiasis, PML, HSV</td>
</tr>
<tr>
<td>&lt;100/cmm</td>
<td>Cerebral Toxoplasmosis, HIV encephalopathy, Cryptococcosis, miliary TB</td>
</tr>
<tr>
<td>&lt; 50/cmm</td>
<td>CMV retinitis, Atypical mycobacteriosis</td>
</tr>
</tbody>
</table>

**A. EMERGENCIES DUE TO OI**

The disease spectrum in HIV infection ranges from acute HIV syndrome, to asymptomatic stage and to full blown AIDS. As the immune system tends to weaken over time, it paves the way for the development of various infection termed opportunistic infections. Consequently, the site of infection determines the clinical presentation and hence, the emergencies that may be encountered often become system specific, though they may involve more than one system.

**PULMONARY EMERGENCIES**

Pneumocystis carinii pneumonia

This disease is caused by the organism pneumocystis. Initially, called pneumocystis carinii, and labelled as protozoa, it has now been established that this is actually a disease caused by pneumocystis jeronii, that is a fungus. The pneumonia caused is primarily an infiltrative pneumonitis and is one of the more commonly encountered emergency.

The most important risk factors for the development of this opportunistic infection are T-cell counts less than 200/ cmm and a history of thrush. The clinical manifestation is sub cute to chronic in the immunocompromised individual and is characterized by the triad of – shortness of breath, fever and non productive cough in most instances. Occasionally,
the cough may be productive, and the manifestations can be complication like pneumothorax or hemoptysis rarely. It may have associated extreme fatigability.

**Prophylaxis for PCP in HIV Positive**

- CD4 Count less then 200/cmm
- Unexplained fever of >37.7°C (100°F) for >two weeks
- History of oropharyngeal candidiasis*
- Previous episode of PCP
- Other AIDS-defining illness

The severity of the disease is important to be established as it often reflects on the management and sometimes the prognosis. The severity is established with the determination of the PaO₂, and based on the PaO₂, the episode of PCP is classified as mild, moderate and severe as shown in Table 3.

Diagnosis should be confirmed by sputum examination, if available. However, treatment should not be withheld for want of confirmation. Serum lactate dehydrogenase (LDH) is often raised. A high LDH level is an unfavourable sign and indicates severe PCP. However, its use as a parameter for diagnosis of the disease is limited. The definitive diagnosis of PCP is confirmed by demonstration of the organism in pulmonary sections. The examination of sputum is a simple, inexpensive, and effective means to confirm the diagnosis. If sputum is not diagnostic, special medical procedures like a bronchoscopy with bronchoalveolar lavage (BAL) may be performed. Special stains may be needed for diagnosis.

The sputum being non productive needs to be induced using the inhalation of hypertonic saline in large number of cases, and stained with Gomori methanamine silver stain. In a center with experienced staff, induced-sputum examination rapidly diagnosed PCP in 80 percent of confirmed cases although rates vary greatly, with sensitivities ranging from 30 to 90 percent. The efficacy for diagnosis using induced cough is 50-80% and with BAL and tracheobronchial biopsy, it is 86-97% and 99% respectively.

Chest X ray may be normal in large number of cases. In some, there may be evidence of pneumothorax, or interstitial infiltration and the radiological findings my correlate to the severity of the disease. The chest film typically shows diffuse interstitial or perihilar infiltrates but can be normal in at least one third of cases.

Pneumatoceles increase the risk of pneumothorax. Less commonly, lobar infiltrates, effusions or cavitary lesions mimic other pulmonary processes (Fig. 1).

Trimethoprim-sulfamethoxazole is the drug of choice for the treatment of PCP. It is given for 21 days followed by prophylactic therapy to prevent the high likelihood of PCP happening again. It has been seen that the dose of 15mg/kg/day of Trimethoprim is as good as the 20 mg/kg/day doses but has lesser side effects. In cases of severe PCP, the use of corticosteroids has clearly decreased clinical failures and lowered death rates. Prednisone is given as 21 day course as: 40 mg BD in first 5 days, 40 mg OD for 6-10 day and 20mg OD from eleventh to twenty first day. Oxygen supplementation should be initiated in cases with moderate and severe PCP.

Primary prophylaxis is recommended in patients with CD4 count <200 cells/mm³, or in the presence of any other AIDS-defining illnesses. Secondary prophylaxis should be given to all patients after an episode of PCP. One double-strength tablet of trimethoprim–sulfamethoxazole (TMP–SMX) (160/800 mg) daily is used for prophylaxis.

**Table 3 : Assessing the severity of pneumocystis jiroveci pneumonia**

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Cough, sweats, exertional dyspnoea</td>
<td>Dyspnoea on minimal exertion, fever, sweats, cough (non productive)</td>
<td>Dyspnoea at rest, tachypnoea, persistent fever</td>
</tr>
<tr>
<td>Blood gas analysis</td>
<td>PaO₂ normal</td>
<td>PaO₂ 60-80 mmHg and falls on exertion</td>
<td>PaO₂ &lt; 60 mmHg</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>Normal or minor perihilar markings</td>
<td>Diffuse bilateral interstitial shadowing</td>
<td>Extensive bilateral interstitial and alveolar markings</td>
</tr>
</tbody>
</table>

(Source: Guidelines for Prevention and Management of Common Opportunistic Infections/Malignancies among HIV-Infected Adult and Adolescent. May 2007, NACO)
observations, as well as follow-up on human immunodeficiency virus (HIV)-infected patients with bacterial pneumonia, and compared pneumococcal pneumonia in patients with and without HIV infection. Fifty five HIV-infected patients, who had had 68 episodes of bacterial pneumonia, were studied prospectively. Twenty one HIV-infected patients with pneumococcal pneumonia were compared to 69 non-HIV-infected patients with pneumococcal pneumonia. Aetiological diagnosis was established in 48 cases (71%). The most common causative agents were S. pneumoniae and H. influenzae. In this study, the overall mortality was 10%. Fifty five percent of patients with follow-up had recurrent episodes.

Presentation can differ substantially from that of an immunocompetent person; a patient with a CD4+ cell count of 20 cmm who has pneumococcal pneumonia will appear much sicker at presentation than one who has no immunosuppression. Most HIV-infected patients with bacterial pneumonia have fever, cough, and sputum production, and the majority will have dyspnea. Patients with PCP present similarly, except that they usually do not produce sputum. Careful history taking also may help distinguish between bacterial pneumonia and PCP. Bacterial infection usually has an acute onset: on average, a patient presenting with bacterial pneumonia has been sick for 2 to 5 days. A patient who presents after 2 weeks of progressive symptoms more likely has PCP, which is more insidious. When taking the patient’s medical history, it is important to ask about all his or her medications, particularly those for pneumonia prophylaxis. Prophylaxis with the combination of trimethoprim and sulfamethoxazole (TMP-SMX) has reduced the incidence of PCP and made it a disease that usually appears only in patients with very low CD4+ cell counts. However, PCP can still develop in a patient receiving PCP prophylaxis. Another important part of the patient’s history regards drug use. The incidence of bacterial pneumonia in HIV-seropositive patients is about 10 times higher than in the HIV-seronegative population. When an HIV-infected patient also has a history of drug abuse, the likelihood of bacterial pneumonia increases.

Diagnosis of the bacterial pneumonia in HIV infected needs to be prompt. Since the radiographic appearance of various pneumonias may overlap, radiographic findings provide only a differential diagnosis,10 not an absolute diagnosis, of the most likely causative organism. The goal is to decide, with some degree of confidence, what the most likely causative organisms are so that the appropriate therapy can be initiated. A lobar infiltrate generally suggests bacterial pneumonia, but it may also represent a fungal infection or even PCP. While diffuse infiltrates are more common in PCP, bacterial infection and tuberculosis (TB) can both result in this radiographic presentation. Linear or nodular infiltrates are associated with fungal, nocardial, and malignant diseases. Mycobacterial infection often shows a localized infiltrate, often apical, with hilar adenopathy. Small nodules may indicate TB, fungal infection, or neoplasm. Larger nodules suggest fungal infection or nodocardial infection, and cavities may represent bacterial infection, fungal infection, TB, or neoplasm. Pleural effusions are most suggestive of bacterial infection but also occur with AIDS-associated malignancies, such as Kaposi’s sarcoma and, rarely, with PCP. Finally, pneumothorax is more commonly seen with PCP than with other infections.

Treatment of bacterial pneumonia in HIV patients is similar to that in HIV-seronegative patients. Therapy should always begin empirically, without waiting for sputum or blood culture results. Results of sputum examination, though useful, often remains controversial.11 Many HIV patients with bacterial pneumonia can be treated as outpatients. Patients with poor immune status, very high fever (above 39.5°C), poor compliance, signs of organ failure, CNS disorders (confusion) and poor vital signs (tachypnea, tachycardia, hypotonia), as well as older patients (above 65 years), should be hospitalized immediately.

For HIV-infected patients in whom bacterial pneumonia is suspected, it is recommended to initiate therapy with a second- or third-generation cephalosporin or β-lactam—lactamase inhibitor, which provides S pneumoniae and H influenzae coverage, or with TMP-SMX. The newer macrolides provide coverage for H influenzae and the atypical pneumonias, such as those caused by Chlamydia and Legionella. However, these are much less common in HIV-seronegative patients; therefore, the use of a macrolide as empiric therapy is not warranted unless these pathogens are suspected. Patients who are already hospitalized are more likely to have a gram-negative infection. In such cases, treatment depends on local resistance patterns and experience.12

The antibiotic selection should include those used to treat patients with Pseudomonas infections; a regimen containing a third-generation cephalosporin plus an aminoglycoside is reasonable. HIV infection does not in itself determine prognosis.

EMERGENCIES DUE TO CNS INVOLVEMENT

There are several neurological manifestation due to which, the HIV infected person may present in the casualty. Many of them have features suggestive of stroke. The common causes are cerebral toxoplasmosis, tubercular meningitis, PML, cryptococcal meningitis, CNS lymphoma etc and are described.

Cerebral toxoplasmosis

Toxoplasma gondii, a parasite, is the most common cause of focal brain lesions in people with AIDS. The definitive host of this parasite is the cat, but the parasite spreads to humans when eggs are ingested in raw or undercooked meats, particularly lamb and pork. Most of the cases are a reactivation disease. The infection may have occurred much earlier, but was kept under control by the healthy immune system. The risk of reactivation increases as the T cells decrease, with the highest risk in persons with T cell counts less than 50.
Patients with cerebral toxoplasmosis complain of headache, confusion or altered mental status, and fever (in about half the cases). Up to 50% of patients with this infection may develop seizures as an initial sign of the disease, and even more will have a stroke. The diagnosis is based on the clinical findings, low T cell count, evidence of the infection in the blood (positive IgG antibodies against Toxoplasma), and CT scan or MRI of the head. CT scan or MRI may reveal typical ring enhancing lesions with a predilection to involve the basal ganglionic region (Fig. 2).

Treatment for cerebral toxoplasmosis consists of a combination of pyrimethamine, sulfadiazine, and folic acid. Alternative therapies for patients with allergies to sulfa drugs include pyrimethamine and folic acid, in addition to one of the following: clindamycin, clarithromycin, dapsone, or azithromycin. Improvement is expected after 7 to 10 days of therapy. The duration of treatment is 4-6 weeks. The presence of multiple brain lesions in a T gondii-seropositive, HIV-infected patient with a CD4 T-cell count <100/µL who is not receiving anti-T gondii prophylaxis is still considered highly predictive of toxoplasmic encephalitis. Neurologic response is noted in 51% of patients by day 3, and in 91% of patients by day 14. Thus, brain biopsy should be considered when there is no clinical improvement by 10-14 days of therapy, or when there is deterioration by day 3. Most patients will also experience radiologic improvement by the third week of treatment. Therefore, neuroradiologic study should be repeated 2-4 weeks after initiation of therapy. Corticosteroids can be administered to patients with toxoplasmic encephalitis with cerebral edema and intracranial hypertension. Duration of corticosteroid administration should be as short as possible (preferably no more than 2 weeks). The outcome of empiric regimens that include steroids should be interpreted with caution; improvement may be caused exclusively by reduction of inflammation or by response of CNS lymphoma to corticosteroid treatment.

If no improvement is seen by then, a brain biopsy is recommended. Cerebral tuberculoma and lymphoma are important differential diagnosis. The secondary prophylaxis with TMP-SMX should be continued till the CD4 sustains a level of over 200/cmm.

Cryptococcal meningitis

Cryptococcus neoformans is the most common fungus responsible for infections in patients with AIDS. The most severe type of cryptococcal infection is chronic meningitis. The symptoms may include headaches, fever, altered mental status, nausea, vomiting, or malaise. All these symptoms usually increase and decrease over the course of 2 or 3 weeks before the diagnosis is made.

A serum cryptococcal antigen test may be used to screen HIV-infected patients with these nonspecific symptoms and low T cell counts. A spinal tap is the preferred diagnostic procedure. The level of cryptococcal antigen in cerebrospinal fluid (CSF) or a CSF fungal culture provides a definite diagnosis (Fig. 3).

Treatment of HIV-associated cryptococcal meningitis is with intravenous amphotericin B for two weeks with or without flucytosine, followed by oral fluconazole for 8 to 10 weeks. Once this therapy is finished, patients will have to stay on suppressive therapy with oral fluconazole. Increased intracranial pressure (pressure inside the head) may be frequent and could be a life-threatening complication of acute cryptococcal meningitis that may require a series of spinal taps or the placement of a special shunt to help relieve pressure.

Treatment success is monitored based on the clinical course and repeated lumbar punctures. CSF is negative in approximately 60% of cases after two weeks. When this is the case, maintenance therapy or secondary prophylaxis can be started, though not sooner than after four weeks of acute therapy. If there is increased intracranial pressure, CSF drainage may become necessary. Steroids are ineffective.

Progressive Multifocal Leukoencephalopathy (PML)

This is a demyelinating disease of the central nervous system, caused by the JC virus. The disease manifests as a result of the reactivation of the virus due to impaired cell mediated immunity. The disease involves demyelination that is multi focal due to the destruction of the cells of myelin sheath, and has a predilection for the white matter of cerebral hemisphere.

PML can occur at any level of immunosuppression. It is more common after the CD4 count falls below 100/cmm, but has been reported even with CD4 count more than
There is a broad spectrum of PML symptoms due to the variety of localized areas of demyelination. Cognitive disorders are frequent and range from mild impairment of concentration to dementia. Additionally, focal neurological deficits are very typical of PML. Mono- and hemiparesis are observed most frequently, as well as speech and even visual deficits. These deficits may be isolated and initially present as discrete changes in coordination, rapidly leading to considerable disabilities. Epileptic seizures may occur. Loss of sensibility, fever, and headache are rare and are should raise a suspicion of cerebral toxoplasmosis.

The diagnosis of PML often requires advanced radiological evaluation. CT scan may not be contributory. MRI is more useful and may reveal small discrete areas of demyelination early in the disease to widespread demyelinated in a hemisphere. It is important to note that often, the lesions are asymmetrical. MRI also helps in differentiating PML from the characteristic findings of cerebral toxoplasmosis or CNS lymphoma.

Specific PML treatment is not available. Numerous strategies such as foscarinet, interferon, immune stimulants and even steroids have been used in past with only modest successes. Cytosine arabinoside is also no longer recommended following the disappointing results of a randomized study. Cidofovir and camptothecin are the two new drugs currently being discussed. However, the results of the controlled studies do not exhibit great success. In the small, usually uncontrolled studies described to date, cidofovir has had positive effects in some, but not all cases. So far, a real benefit has not been proven. The absolute priority should currently be to optimize ART in cases of PML. It was supported in past by numerous studies that progression significantly improved under HAART. This has been confirmed by several other groups. As synergism between HIV and JCV has been demonstrated in vitro, maximal HIV suppression should at least be achieved. Although progression of disease has been described under sufficient antiretroviral therapy, HAART often remains the only real hope for patients today (Table 4).

A recent study has shown that JC virus DNA levels in cerebrospinal fluid of patients with HIV associated progressive multifocal leucoencephalopathy has prognostic significance.

**Tubercular Meningitis**

Extrapulmonary tuberculosis occurs predominantly in co-infected patients with CD4+ T-cell counts of less than 200/µl. The most common feature of extrapulmonary tuberculosis is cervical lymphadenopathy. Tuberculous meningitis often presents with unspecific prodromal symptoms, such as headache, nausea and vomiting followed by elevated temperature and clinical signs of meningeal irritation. The basal meninges are usually involved and cranial palsies of the IIIrd and VIth nerves are common. Mono-, hemi-, or paraparesis as well as seizures can occur. In case of doubt, a lumbar puncture should be performed without delay. The diagnosis is established with a lumbar puncture. The pressure is high, the protein elevated, the sugar low. There is a pleocytosis with predominantly lymphocytes. Acid fast staining may not demonstrate the organisms. Cultures take several weeks.

Anti tuberculous therapy with the standard drugs should be given for 1 year.

Treatment of TBM follows in line with the treatment of the TB in HIV sero negative individuals. The national guidelines for India recommend anti tuberculous therapy with the standard drugs to be given for 1 year.

As TBM belongs to WHO Stage IV for HIV, the anti retro viral therapy should be initiated as soon as possible, correlating with the CD4 levels. There is considerable drug interaction between various classes of the ARV and the ATT. The changes in drug levels need to be addressed adequately to prevent sub optimal treatment.

**Primary CNS lymphoma**

Primary CNS Lymphoma is rare in the general community, but affects about 2% of AIDS patients. Survival after diagnosis is usually limited to a few months only. It is a typical end-stage complication of HIV disease. Evolution of disease is over 2-8 weeks. It usually occurs when CD4 count is <100. Disease progresses over a few weeks. Patients are afebrile, with headache and focal neurological deficits (confusion, hemiplegia, seizures). They may presents with mental status changes (60%), personality or behavioral changes. Seizures occur in 15%. CT scan/MRI show peri-ventricular irregular lesions which appear solid on enhancement in one or more sites. There is prominent edema. Lymphoma is suspected when there is a negative toxoplasma IgG or failure to respond to empiric toxoplasma treatment. Neuropsychological tests show subcortical dementia. Mini-mental status examinations are not very sensitive. CSF analysis is normal in 30-50%. Cytology is positive in <5%.

There is no cytotoxic chemotherapy for this disease. Irradiation can help some patients, but is considered palliative. Corticosteroids can also help some patients.

**DIARRHEAL DISEASES IN HIV**

Diarrhoea is among the most common symptoms of HIV infection and is experienced by over 90% of patients with AIDS. It becomes more frequent as immune deficiency...
progresses. Some of these diarrhoeal diseases are likely to be severe, recurrent and persistent, and associated with extra-intestinal disease. Diarrhoea and weight loss are independent predictors of mortality. Enteric pathogens recovered from HIV-infected persons include: Shigella flexneri, other Shigella spp., Salmonella spp., Campylobacter spp., enterohemorrhagic E. coli, enteroinvasive E. coli, Clostridium difficile, Vibrio cholerae, Staph. aureus, Plesiomonas shigelloides, Aeromonas hydrophila and Yersinia enterocolitica (Table 5).

Diarrhoea in HIV-infected individuals may be either acute (<7 days), or chronic (three or more liquid stools daily for >14 days).12 Chronic diarrhoea leads to malabsorption, malnutrition and contributes to mortality. Initial clinical evaluation should include assessment of hydration, skin elasticity, weight, pulse, blood pressure, respiration, eyes, mucous membranes and urine output. Chronic diarrhoea is a very frequent and frustrating problem in PLHA; at least 50% experience it sometime during the evolution of the disease. One recently conducted study has reported that 32% of the people had diarrhoea as the presenting feature.29 Diarrhoea is often accompanied by nausea, weight loss, abdominal cramps and dehydration. There is often an intermittent watery diarrhoea, without blood or mucus. In one-third to two-thirds of cases, no cause is identified. Wherever possible, establish the cause and give specific treatment. The step-up diagnostic approach consists of examination of the stool for ova and parasites (with special stains – modified AFB, trichome and monoclonal stains) and endoscopic biopsy (gastroscopic/colonoscopic) if referred. The key to good management is rehydration including replacement of electrolytes. High-energy and high-protein intake reduces the degree of muscle wasting.

Prevention consists of attention to personal hygiene, hand-washing, drinking boiled water and eating only thoroughly cooked meat and vegetables.

An overview of the common causative opportunistic agents and the management is provided in the following Table 6.

One of the studies from Tehran30 evaluated cryptosporidial diarrhea in HIV infected as well as in acute myeloid leukemia. They reported an overall, 1.4% of all patients and 6.3% of diarrheal patients were infected by Cryptosporidium. The results revealed three cases of cryptosporidiosis, including two cases of acquired immunodeficiency syndrome (AIDS) and one of acute myeloid leukemia (AML). The prevalence of infection in subjects with AIDS or AML who were suffering from diarrhea was 33.4% and 11.1%, respectively. The duration of disease in infected patients lasted for weeks, and was terminated by death in two AIDS patients. In the patient with AML, diarrhea lasted for 18 days, and stopped after discontinuation of immunosuppressive therapy.

Basic Principles in the management of HIV gut infection: As evidenced, there are wide spectrum of organisms that can infect the gut. However, some important considerations always should be kept in mind:

Principles of managing gut infection in HIV infected individuals: Point to remember:

- Remember more than one pathogens may be involved concurrently
- Dissemination from the gut can occur in some bacterial infections (MAC, Salmonella, Shigella, Campylobacter)
- Relapse following successful treatment is frequent (CMV, Salmonella, Shigella, Campylobacter, MAC, Cryptosporidium, microsporidia, Cyclospora)
- Progressive weight loss and reduced performance status are frequent if there is no resolution of diarrhea & pathogen is not identified. The symptomatic therapy is indicated.

**OCULAR EMERGENCIES**

Ocular disorders associated with HIV disease remain important problems, despite HAART. Amongst the various ocular manifestations of HIV, the two condition that need to be promptly identified and treated are:- Cyto megalovirus infection and varicella zoster infection.

The approach to management of CMV retinitis has evolved from short-term treatment of a preterminal infection to the long-term management of what has become a chronic disease.31

**Cytomegalovirus infection**

It is the most common ocular fatality. It can occur as pre ART OI or as an immune reconstitution manifestation. It usually occurs with CD4 less than 50 /cmm. When occurring as an IRS, it typically, like any other IRS, should appear anytime between 6 weeks to 6 months of initiation of ART. Prior to the advent of highly active antiretroviral therapy (HAART), almost one-third of people with AIDS developed CMV retinitis during their lifetime.32 Certain studies have documented the existence of this disease as high and leading to blindness in 30% of the infections. These were more commonly reported in people who were not diagnosed to have HIV infection in past, but this episode

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Table 5 : Etiological agents for diarrhea in HIV infected

<table>
<thead>
<tr>
<th>Etiological agents</th>
<th>Small bowel (duodenum/jejunum)</th>
<th>Large bowel (colon/terminal ileum)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria</strong></td>
<td>Campylobacter species, Yersinia species, Clostridium difficile</td>
<td></td>
</tr>
<tr>
<td>Cryptobacterium avium complex, Salmonella species</td>
<td>Aeromonas species, Entamoeba histolytica</td>
<td></td>
</tr>
<tr>
<td><strong>Protozoa</strong></td>
<td>Cryptosporidium species, Microsporidia, Cyclospora species, Giardia lamblia</td>
<td></td>
</tr>
<tr>
<td><strong>Viruses</strong></td>
<td>Rotavirus, Astrovirus, Calicivirus, Picornavirus, HIV</td>
<td>Adenovirus, Herpesvirus, Cytomegalovirus</td>
</tr>
</tbody>
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was the one that raised high index of suspicion for the HIV infection in them. Almost all homosexual or bisexual men and more than 75% of all HIV-infected people carry the virus. A small percentage with severely compromised immune systems actually develops CMV disease when immunosuppression reactivates inherent CMV to cause disseminated or localized endorgan disease.

The manifestation of retinitis are due to reactivation of the CMV infection and symptomatically leads to blind spots, visual field loss, flashing lights, floaters, or decreased or blurred vision. Peripheral retinal lesions may be asymptomatic, but the central lesions on the macula leads to development of decreased acuity of vision and central field defects.

Diagnosis of CMV retinitis can readily be made by fundoscopy performed by an experienced ophthalmologist. The fundus examination reveals peripheral, whitish exudates. These should not be confused with the cotton wool spots that are sometimes seen with patients with high HIV levels. The bilateral involvement is not very commonly seen. There is often perivascular fluffy yellow–white retinal infiltrates, and focal necrotizing retinitis with or without intraretinal haemorrhage. In the absence of HAART or specific anti-CMV therapy, retinitis progresses and causes a characteristic brushfire pattern, usually within 10–21 days after presentation. A granular, white leading edge forms, eventually resulting in an atrophic and gliotic scar leading to blindness. In patients with CD4 count more than 100/cmm, CMV is less likely and other causes should be looked for. CMV infection usually does not cause vitritis, though, it have been sometimes observed in vitritis associated with immune reconstitution syndrome. The presence of IgG antibodies against CMV is not diagnostic. However, a positive CMV PCR and positive antibodies to pp65 may help in establishing the diagnosis of CMV retinitis. However, these investigations are routinely not available and clinical, fundus examination and low CD4 count remain the helpful indices for suspecting CMV retinitis in HIV infected individual (Fig. 4).

It is important to understand that none of the medicines used in the treatment of CMV retinitis reverses the disease. They are only helpful in halting the diseases progression, and hence, time is vital in treating and preventing blindness. The drugs used are gancyclovir, foscarnet and cidofovir. However, their availability as well as availability of trained...

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<tr>
<th>Organism</th>
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<tr>
<td>Cryptosporidiosis</td>
<td>Acid-fast stain of stool; oocysts 4-5 um; monoclonal antibody study of stool</td>
<td>Azithromycin 600 mg/d orally plus paromomycin 1 g twice daily orally for 4 weeks followed by paromomycin alone</td>
<td>Atovaquone 750 mg twice daily orally</td>
<td>minocycline and pyrimethamine synergistic in vitro with the macrolides</td>
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<tr>
<td>Microsporidiosis enterocytozoon bieneusi</td>
<td>Chemofluorescent, giemsa, or trichrome stain of stool</td>
<td>Albendazole 400-800 mg orally twice daily for 30 days, then 200-400 mg/d orally for maintenance</td>
<td>Atovaquone 750 mg twice daily orally</td>
<td>Albendazole gives only symptomatic relief</td>
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<td>Isosporiasis</td>
<td>Acid-fast stain of stool; oocysts 30 x 12 um</td>
<td>TMP-SMX Ds orally four times daily for 2-4 weeks, then twice daily for maintenance</td>
<td>Pyrimethamine 75 mg/d orally for one month with folinic acid</td>
<td>—</td>
</tr>
<tr>
<td>Cyclospora infection</td>
<td>Acid-fast stain of stool; oocysts 8-10 um</td>
<td>TMP-SMX DS orally twice daily for 10 days, followed by once orally three times weekly for maintenance</td>
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<tr>
<td>Giardiasis</td>
<td>Stool ova and parasites, monoclonal antibody test, or Giardia antigen test</td>
<td>Metronidazole 250 mg orally three times daily for 5-10 days or albendazole 400 mg orally daily for 5 days</td>
<td>Tinidazole 2 g orally (one-time dose) or quinacrine 100 mg orally three times daily for 5 days</td>
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<td>Entamoeba histolytica</td>
<td>Stool ova and parasites</td>
<td>Metronidazole 750 mg orally three times daily for 10 days or tinidazole 2 g/d orally for 3 days</td>
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<td>Acute treatment is followed by iodoquinol 650 mg orally three times daily for 20 days or paromomycin 500 mg orally three time daily for 7 days</td>
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<td>Strongyloides stercoralis</td>
<td>Stool ova and parasites</td>
<td>Albendazole 400 mg/d orally for 3 days or ivermectin 200 ug/kg/d orally given once</td>
<td>Thiabendazole 25 mg/kg orally twice daily for 2 days</td>
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(Ref: NACO Guidelines for Prevention and Management of Common Opportunistic Infections/Malignancies among HIV-Infected Adult and Adolescent, May 2007.)
pain, tingling, numbness, itching or aching in or under the skin of one side of the body or face. However, sometimes, the infection may affect the visceral organs spreading to lungs, liver or nervous system. When the ophthalmic division of the trigeminal nerve is involved, it may lead to dangerous affliction of the eye.

Maintenance therapy is intended to prevent the virus from causing a relapse. This may be discontinued once the CD4 count increases to more than 200 cells/mm^3 for at least 6 months following HAART. The treatment of choice is ganciclovir 5 mg/kg twice daily IV (induction) followed by capsules (maintenance), and can treat all forms of CMV disease. IV ganciclovir is given twice daily for two to three weeks and then IV once daily 5–7 days a week. Oral treatment is given as 1000 mg capsules three times daily.

Varicella Zoster Infection

It is caused by the Varicella zoster virus (VZV) or herpesvirus type 3. Herpes zoster occurs in 8–11% of HIV-infected individuals. The incidence of herpes zoster is 15–25 times higher in HIV-1-infected persons than in the general population. The symptoms of zoster start with a burning, sharp pain, tingling, numbness, itching or aching in or under the skin of one side of the body or face. However, sometimes, the infection may affect the visceral organs spreading to lungs, liver or nervous system. When the ophthalmic division of the trigeminal nerve is involved, it may lead to dangerous affliction of the eye.

The infection with Varicella zoster is the second most common infection that may be an ocular emergency. It can present as

- acute retinal necrosis (a rapid deterioration of the retina) that can occur at any stage of HIV infection.
- The second syndrome occurs in patients with T cell counts typically less than 50 and is known as progressive outer retinal necrosis syndrome. Approximately two thirds of patients with this disease will develop it in both eyes. This disease is different from acute retinal necrosis syndrome. The treatment for this form of Varicella zoster retinitis is difficult and seems not to respond to intravenous acyclovir or other forms of treatment with one medication only. A majority of patients (70%) with this syndrome will develop retinal detachment resulting in poor vision.

Treatment is usually intravenous acyclovir 10 mg/kg q8h and is given for 7–10 days and continued until the lesions are clearly resolving.

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